Attorney Docket: 100715.52872US
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Jan-Maarten VERBEEK, et al.

Serial No.: not yet assigned

Filed: November 14, 2003

Title: PROCESS FOR PREPARATION OF IMIDAZOLYL COMPOUNDS

CLAIM OF CONVENTION PRIORITY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Priority is hereby claimed based on the following foreign patent application:
European Patent Application No. 02079838.5,
filed November 18, 2002,
and
Netherlands Patent Application No. 1021939,
Filed November 18, 2002,
and it is respectfully requested that the instant application be accorded the benefit of the filing dates of said foreign applications pursuant to the provisions of 35 U.S.C. §119.

In support of this claim, duly certified copies of said foreign applications are submitted herewith.

Respectfully submitted,

November 14, 2003

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Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

02079838.5

Der Präsident des Europäischen Patentamts:
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

Anmeldung Nr:
Application no.: 02079838.5
Demande no:

Anmeldetag:
Date of filing: 18.11.02
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Novel process for the preparation of imidazolyl compounds

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07D233/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SK TR

SPW02.12

Novel Process for the preparation of imidazolyl compounds.

The present invention relates to a process for the preparation of imidazolyl compounds.

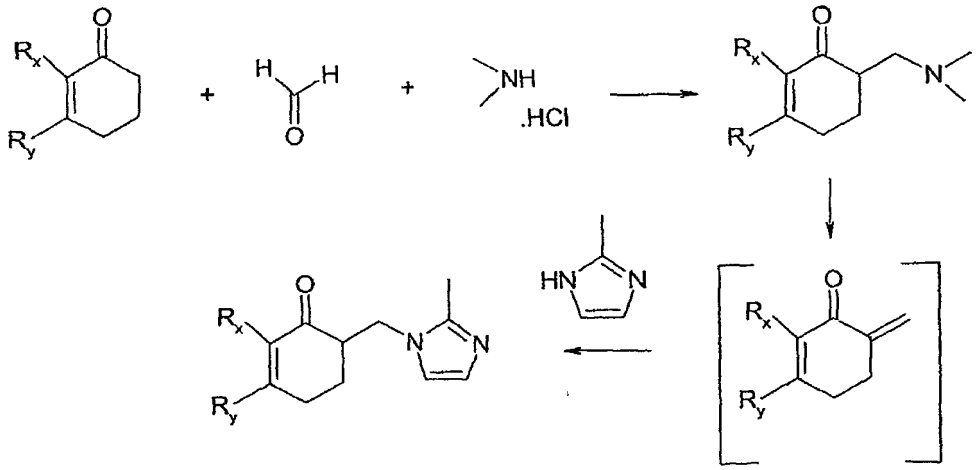
1,2,3,9-Tetrahydro-9-methyl-3-[2-methyl-1*H*-imidazol-1-yl)methyl]-4*H*-carbazol-4-one (ondansetron) is known from EP191562 and US4,695,578. In these patent publications a general class of compounds including ondansetron and homologous compounds, their preparation and their use as potent selective antagonists at "neuronal" 5-hydroxytryptamine receptors and their use in the treatment of migraine and psychotic disorders is described.

(10R)-5,6,9,10-Tetrahydro-10-[(2-methyl-1*H*-imidazol-1-yl)methyl]-4*H*-pyrido[3,2,1-jk]-carbazol-11(8*H*)-one (cilansetron) (also known as (R)-(-)-4,5,6,8,9,10-hexahydro-10-[(2-methyl-1H-imidazol-1-yl)methyl]-11H-pyrido-[3,2,1-jk]-carbazol-11-one) is known from EP-B-0297651, from EP-B-0601345 and from EP-B-702594. In the first patent publication a general class of compounds, including cilansetron and homologous compounds, their preparation and their use as 5-HT antagonists is described. The second patent publication describes the use of a selection of these type of compounds for the treatment of certain diseases and the third the preparation of enantiomerically pure compounds and their hydrochloride monohydrate.

It is a common feature of the above compounds that they contain a substituted imidazolyl group attached to the α-place with regard to the keto group of the carbazole system with a methylene bridge. Several possibilities for the synthesis of these compounds are described in the mentioned patent publications. It is a common feature in these syntheses that the substituted imidazolyl group is introduced by means of a Mannich reaction, followed by a deamination to yield an intermediate exomethylene compound which is reacted with the substituted imidazolyl group (see scheme 1 for an example).

A drawback of this route is that the yield in this sequence of reaction steps is rather low. In US 4,695,578 the first step which is normally giving the lowest yield is not described and the second step (Example 7 of US 4,695,578) gives a yield of 68%. In EP-B-0297651 the first step (Example 1c of EP-B-0297651) has a yield of 53% and the second step (Example 1d of EP-B-0297651) a yield of 87%. During up-scaling it

appeared that this route gives rise to the formation of a considerable amount of tarlike side-products.

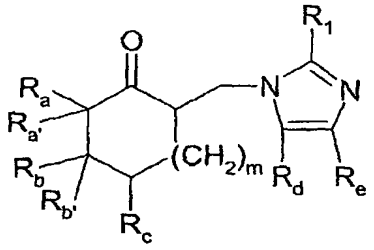


Scheme 1.

It is the objective of the present invention to provide an alternative process to prepare imidazolyl-compounds which process should be economically operative and meet one or more of the following requirements: a) a relatively high yield, b) short reaction times compared with prior art processes, c) less side reactions, d) higher quality of the final product and e) using non-diluted reaction conditions and an environmentally acceptable solvent.

It has surprisingly been found that these type of imidazolyl compounds can easily be prepared using a substituted oxazolidine compound for the introduction of the methylene bridge.

Therefore the present invention relates to a method for the preparation of an imidazolyl compound of the general formula



(I)

wherein:

R_a and R_b each separately are $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$ alkoxyalkyl, optionally substituted aryl or heteroaryl;

or wherein R_a and R_b together form a further homocyclic or heterocyclic system comprising one or more rings;

$R_{a'}$ and $R_{b'}$ each are hydrogen or together form a carbon-carbon double bond, said carbon-carbon double bond optionally being part of an aromatic system;

R_c is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxyalkyl or halogen;

R_d is hydrogen or $(C_1\text{-}C_4)$alkyl;

R_e is hydrogen or $(C_1\text{-}C_4)$alkyl;

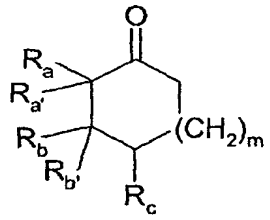
m is 1 or 2; and

R_1 is hydrogen or $(C_1\text{-}C_4)$alkyl;

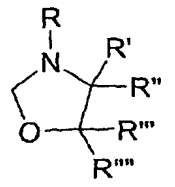
as well as its acid addition salt;

characterized in that a compound of the general formula

(II)



is reacted with a compound of the formula



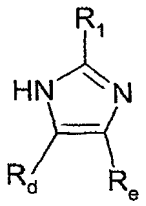
(III)

wherein:

R is a hydrogen, a (C_1-C_4)alkyl group optionally substituted with a hydroxygroup or an optionally substituted aryl group,

R', R", R'" and R"" each individually are a hydrogen or a (C_1-C_4)alkyl group;

followed by a reaction with a compound of the formula



(IV)

wherein R_1, R_d and R_e have the meanings defined above;
and optionally followed by a reaction with a suitable acid.

Alkyl groups of the present invention include straight-chained, branched and cyclic alkyl radicals containing up to 6 carbon atoms. Suitable alkyl groups may be saturated or unsaturated. Further, an alkyl group may also be substituted one or more times with substituents selected from the group consition of aryl, halo, hydroxy, cyano or one- or di-alkyl substituted amino.

Aryl groups of the present invention include aryl radicals which may contain up to 6 hetero atoms. An aryl group may also be optionally substituted one or more times with an substituent selected from the group consistion of aryl, (C_T-C_6) alkyl, halo, hydroxy, cyano or one- or di-alkyl substituted amino, and it may be also fused with an aryl group or cycloalkyl rings. Suitable aryl groups include, e.g. phenyl, naphtyl, tolyl, imidazolyl, pyridyl, pyrroyl, thienyl, pyrimidyl, thiazolyl and furyl groups.

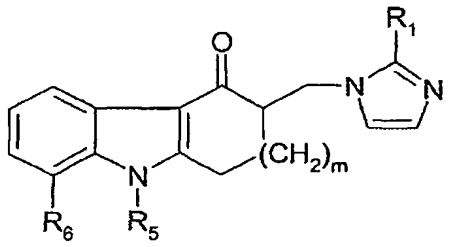
With a homocyclic system is meant a system containing at least one saturated or unsaturated cyclic group containing only carbon atoms and hydrogen atoms.

With a heterocyclic system is meant a system containing at least one saturated or unsaturated cyclic group containing also one or more heteroatoms such as N, O or S.

Both the homocyclic and heterocyclic system may optionally be substituted with a substituent selected from the group consisting of alkyl, aryl , cyano, halogen, hydroxy or one- or di-alkyl substituted amino.

In a preferred embodiment of the invention R_c is hydrogen or (C_1-C_6)alkyl, R_d is hydrogen or (C_1-C_4)alkyl; R_e is hydrogen or (C_1-C_4)alkyl; and R_1 is hydrogen, methyl or ethyl.

The reaction according to the invention is especially useful for the preparation of compounds of the general formula



(Ia)

wherein:

m is 1 or 2;

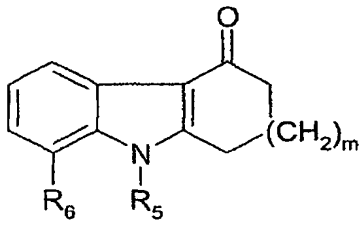
R_1 is hydrogen, methyl or ethyl; and

R_5 is a (C_1-C_4) alkyl;

R_6 is a hydrogen or a (C_1-C_4)alkyl, or

R_5 and R_6 together with the intermediate atoms form a 5, 6, or 7 membered ring, optionally substituted with one or two substituents selected from the group consisting of halogen, hydroxy, (C_1-C_4)alkyl, (C_1-C_4)alkoxyalkyl and (C_1-C_4)alkoxy.

In this case the starting compound is a compound of the general formula



(IIa)

This compound is further referred to as a carbazolone compound.

Preferred compounds of the general formula Ia are the compound wherein m=1 and R_5 and R_6 together with the intermediate atoms form a 6-membered ring and the compound wherein m=1, R_5 is methyl and R_6 is hydrogen. For the first compound the yield for the process starting with 5,6,9,10-tetrahydro-4*H*-pyrido[3,2,1-jk]carbazol-11(8*H*)-one and 3-oxazolidineethanol is 77% (see Example 2) compared with the overall yield of 46% in the process according to EP0297651 (Examples Ic and Id). Higher yields may be obtained at a production scale.

In the substituted oxazolidine preferably one of the R' and R" and one of the R"' and R"" is hydrogen, as an oxazolidine disubstituted on the same carbon atom, such as 4,4-dimethyloxazolidine gives a lower yield in the reaction. Preferred oxazolidines are 3-oxazolidineethanol and 3-ethyl-oxazolidine. The most preferred oxazolidine is 3-oxazolidineethanol.

The reaction has to be performed in acidic medium and the grade of acidity depends on the activation of the system that has to react. In the case of carbazolone systems the medium should be highly acidic. Examples of suitable acids in the last case are methanesulfonic acid, trifluoromethanesulfonic acid, p-toluenesulfonic acid and HCl gas in alcoholic medium.

In order to get a high yield the reaction solution should contain a low amount of water. The amount of water should preferably be below 0.6% (V/V), more preferably below 0.3 % V/V and most preferably below 0.1% V/V.

The optimal reaction temperature is dependent on the starting materialand the solvent and differs for the two reaction steps. The first step of the reaction can be performed between 40°C and 110°C. For the carbazolone systems the preferred reaction temperature in the first step is between 50°C and 90°C and the most preferred temperature is approximately 70°C. The second step can generally be performed between 100°C and 140°C. For the carbazolone systems the preferred reaction temperature in the second step is between 110°C and 130°C and the most preferred temperature is approximately 120°C.

The reaction can be performed in different solvents such as dipolar aprotic solvents like DMF or in alcohols. Preferred solvents are C_4-C_7 alcohols and the choice may depend on the desired reaction temperature. Examples of suitable alcohols are 1-butanol, 1-hexanol and isoamyl alcohol. A preferred alcohol is 1-butanol. Also suitable are mixtures of aromatic hydrocarbons and alcohols, such as mixtures of toluene and an alcohol and monochlorobenzene and an alcohol. A preferred mixture is a mixture of monochlorobenzene and methanol. When solvent mixtures are used the lower boiling solvent can be distilled off before the second step in order to reach higher reflux temperatures of the solvent system in the second step.

The ratio of the solvent volume to the amount of reactants in the mixture can be varied over a relatively broad range and depends on the solubility of the reactants. In general the ratio of the amount of solvent to the amount of reactants can typically be about 1 : 1 to 15 :1, where the ratio is expressed as the volume of solvent relative to the weight of the reactants in the solvent. Preferably the ratio is about 1:1 to about 10 :1. In the case of the carbazolone systems the preferred ratio of the volume of solvent to the weight of reactants is about 4:1.

The products obtained can be crystallized from different solvents. Examples of solvents for the cyrstallisation of free bases are aromatic hydrocarbons such as toluene. The hydrochloric acid salts can e.g. be crystallized from alcoholic solvents, such as isopropanol or 1-butanol.

The following examples are only intended to further illustrate the invention, in more detail, and therefore these examples are not deemed to restrict the scope of the invention in any way.

Example 1: Materials and Methods

5,6,9,10-Tetrahydro-4*H*-pyrido[3,2,1-jk]carbazol-11(8*H*)-one was made according to EP0375045. 3,4-Dihydro-1(2*H*)-naphthalenone was obtained from a commercial source. 1,2,3,9-Tetrahydro-9-methyl-4H-carbazol-4-one was made according to US 3,892,766 from Warner-Lambert Company and Elz, S. and Heil, W., Bioorganic & Medicinal Chemistry Letters 1995, 5, 667-672. Methanesulfonic acid was obtained from a commercial source.
NMR spectra were measured on a Varian VXR 200 and MS spectra on a Finnigan TSQ 7000 . HPLC analyses were performed on a HP1050 system with a Separations 757 detector (250 nm) and a Separations Marathon XT column oven at 35 °C. The column used was a Zorbax XDB C8 colomn 15x0.3 cm. The eluens was prepared as follows: mix 2 l water, 2 ml triethylamine and 5 ml 25% ammonia, buffer it at pH=4 with formic acid and add 0.5 l acetonitril. The flow was 1 ml/min.

Example 1a: Preparation of oxazolidines.
3-Oxazolidineethanol was made as follows:
Equimolair amounts of diethanolamine and paraformaldehyde in 1-butanol were heated to 70°C. After 1 hour reaction time the water formed was removed by azeotropic distillation with 1-butanol.

3-Ethyl-oxazolidine was made according to Heany, H. et al., Tetrahedron 1997, 53, 14381-96.

4,4-Dimethyl-oxazolidine is commercially available and was purchased as a 75% w/w solution in water. The 4,4-dimethyl-oxazolidine was extracted from the water layer by washing with dichloromethane/ saturated NaCl-solution. The dichloromethane layer was dried on anhydrous sodium sulfate and subsequently evaporated.

Example 2. Reaction of 5,6,9,10-tetrahydro-4*H*-pyrido[3,2,1-jk]carbazol-11(8*H*)-one with 3-oxazolidineethanol.

5,6,9,10-tetrahydro-4*H*-pyrido[3,2,1-jk]carbazol-11(8*H*)-one (25.00 g ≡ 111.0 mmole) and methanesulfonic acid (17.06 g ≡ 177.5 mmole) in 1-butanol (100 ml) were heated to 70°C. In 3 minutes a solution was added of 3-oxazolidineethanol (19.49 g ≡ 166.4 mmole) in 1-butanol (39 ml).
After 50 minutes at 80°C 2-methylimidazole (45.55 g ≡ 554.8 mmole) was added. After 1.5 hours at 120°C the reaction mixture was partly evaporated till 30 ml of 1-butanol was left over.
At 70°C, 75 ml of toluene and 50 ml of water were added to the residue. The layers were separated. The water layer was extracted with 75 ml of toluene. The combined toluene layers were washed three times with 100 ml of water.
The organic layer was evaporated to dryness and subsequently 125 ml of 1-butanol was added. To the resulting solution 12.5 ml of 36% m/m hydrochloric acid was added. After stirring for 2 hours at room temperature the formed solid was filtered off and washed with 1-butanol and MTBE. Yield after drying: 30.40 g (77.0%) 5,6,9,10-tetrahydro-10-[(2-methyl-1*H*-imidazol-1-yl)methyl]-4H-pyrido[3,2,1-jk]carbazol-11(8*H*)-one hydrochloride (77.0%). HPLC: ≥ 95%. ^{1}H NMR [200 MHz, DMSO-d^6:$CDCl_3$ 4:1] δ 1.97(1H,m), 2.18 (3H,m), 2.68(3H,s), 2.95(2H,t), 3.00(1H,dd), 3.12(2H,m), 4.13(2H,m), 4.29(1H,dd), 4.66(1H,dd), 6.97(1H,d), 7.09(1H,t), 7.55(1H,d), 7.68(1H,d) and 7.71(1H,d). MS [ESI] MH^+ = 320.

Exampl 3. Reaction of 5,6,9,10-tetrahydro-4*H*-pyrido[3,2,1-jk]carbazol-11(8*H*)-on with 4,4-dimethyl-oxazolidine.

5,6,9,10-tetrahydro-4*H*-pyrido[3,2,1-jk]carbazol-11(8*H*)-one (20.00 g≡ 88.8 mmole) and methanesulfonic acid (13.65 g≡ 142.0 mmole) in 1-butanol (60 ml) were heated to 70°C. In 2 minutes 4,4-dimethyl-oxazolidine (13.47 g≡ 133.2 mmole) in 1-butanol (10 ml) was added.

After 50 minutes at 80°C 2-methylimidazole (36.45 g ≡ 444.0 mmole) was added. After 2 hours at 120°C the reaction mixture was partly evaporated till 20 ml of 1-butanol was left over.

At 70°C, 60 ml of toluene and 40 ml of water were added to the residue. The layers were separated. The water layer was extracted with 60 ml of toluene. The combined toluene layers were washed three times with 80 ml of water.

The organic layer was evaporated to dryness and subsequently 100 ml of 1-butanol was added. To the resulting solution 10.0 ml of 36% m/m hydrochloric acid was added. After stirring for 2 hours at room temperature the formed solid was filtered off and washed with 1-butanol and MTBE. Yield after drying: 12.38 g 5,6,9,10-tetrahydro-10-[(2-methyl-1*H*-imidazol-1-yl)methyl]-4*H*-pyrido[3,2,1-jk]carbazol-11(8H)-one hydrochloride (39.2%). HPLC: ≥ 95%. ^{1}H NMR and MS: see Example 2. The mother liquor contained 3.45 g (10.9%) of product.

Example 4. Reaction of 5,6,9,10-tetrahydro-4*H*-pyrido[3,2,1-jk]carbazol-11(8*H*)-one with 3-ethyl-oxazolidine.

5,6,9,10-tetrahydro-4H-pyrido[3,2,1-jk]carbazol-11(8H)-one (20.00 g≡ 88.8 mmole) and methanesulfonic acid (13.65 g≡ 142.0 mmole) in 1-butanol (60 ml) were heated to 70°C. In 2 minutes 3-ethyl-oxazolidine (13.46 g≡ 133.2 mmole) in 1-butanol (10 ml) was added.

After 50 minutes at 80°C 2-methylimidazole (36.45 g ≡ 444.0 mmole) was added. After 2 hours at 120°C the reaction mixture was partly evaporated till 20 ml of 1-butanol was left over.

At 70°C, 60 ml of toluene and 40 ml of water were added to the residue. The layers were separated. The water layer was extracted with 60 ml of toluene. The combined toluene layers were washed three times with 80 ml of water.

The organic layer was evaporated to dryness and subsequently 100 ml of 1-butanol was added. To the resulting solution 10.0 ml of 36% m/m hydrochloric acid was added. After stirring for 2 hours at room temperature the formed solid was filtered off and washed with 1-butanol and MTBE. Yield after drying: 22.10 g (70.0 %) 5,6,9,10-tetrahydro-10-[(2-methyl-1*H*-imidazol-1-yl)methyl]-4H-pyrido[3,2,1-jk]carbazol-11(8*H*)-one hydrochloride (70.0%). HPLC: ≥ 95%. ^{1}H NMR and MS: see Example 2.

Example 5. Reaction of 3,4-dihydro-1(2*H*)-naphthalenone with 3-oxazolidineethanol.

3,4-dihydro-1(2*H*)-naphthalenone (12.98 g≡ 88.8 mmole) and methanesulfonic acid (13.65 g≡ 142.0 mmole) in 1-butanol (60 ml) were heated to 50°C. In 2 minutes a solution was added of 3-oxazolidineethanol (15.59 g≡ 133.1 mmole) in 1-butanol (14 ml).
After 50 minutes at 80°C 2-methylimidazole (36.45 g ≡ 444.0 mmole) was added. After 2 hours at 120°C the reaction mixture was partly evaporated till 20 ml of 1-butanol was left over.
At 70°C, 60 ml of toluene and 40 ml of water were added to the residue. The layers were separated. The water layer was extracted with 60 ml of toluene. The combined toluene layers were washed three times with 80 ml of water.
The organic layer was evaporated to dryness and subsequently 100 ml of 1-butanol was added. To the resulting solution 10.0 ml of 36% m/m hydrochloric acid was added. The resulting solution was evaporated till an end volume of 60 ml. After stirring for 2 hours at room temperature the formed solid was filtered off and washed with 1-butanol and MTBE. Yield after drying: 15.28 g (62.2%) 3,4-dihydro-2-[(2-methyl-1H-imidazol-1-yl)methyl]-1(2H)-naphthalenone hydrochloride. HPLC: ≥ 95%. ^{1}H NMR[200 MHz, DMSO-d^6:$CDCl_3$ 4:1] δ 2.00 (2H,m), 2.73 (3H,s), 3.20 (3H,m), 4.27 (1H,dd), 4.68 (1H,dd), 7.35 (2H,t), 7.55(2H,m), 7.70 (1H,d) and 7.90 (1H,d). MS [ESI] MH^+ = 241. The mother liquor contained 3.28 g (13.3%) of product.

Example 6. Reaction of 3,4-dihydro-1(2*H*)-naphthalenone with 4,4-dimethyl-oxazolidine.

3,4-dihydro-1(2*H*)-naphthalenone (12.98 g≡ 88.8 mmole) and methanesulfonic acid (13.65 g≡ 142.0 mmole) in 1-butanol (60 ml) were heated to 70°C. In 2 minutes 4,4-dimethyl-oxazolidine (13.46 g≡ 133.1 mmole) in 1-butanol (10 ml) was added. After

50 minutes at 80°C 2-methylimidazole (36.45 g ≡ 444.0 mmole) was added. After 2 hours at 120°C the reaction mixture was partly evaporated till 20 ml of 1-butanol was left over.

At 70°C, 60 ml of toluene and 40 ml of water were added to the residue. The layers were separated. The water layer was extracted with 60 ml of toluene. The combined toluene layers were washed three times with 80 ml of water.

The organic layer was evaporated to dryness and subsequently 100 ml of 1-butanol was added. To the resulting solution 10.0 ml of 36% m/m hydrochloric acid was added. The resulting solution was evaporated till an end volume of 50 ml. After stirring for 2 hours at 0°C the formed solid was filtered off and washed with 1-butanol and MTBE. Yield after drying: 14.13 g (57.5%) 3,4-dihydro-2-[(2-methyl-1H-imidazol-1-yl)methyl]-1(2*H*)-naphthalenone hydrochloride. HPLC: ≥ 95%. ^{1}H NMR and MS: see Example 5. The mother liquor contained 2.33 g (9.5%) of product.

Example 7. Reaction of 3,4-dihydro-1(2*H*)–naphthalenone with 3-ethyl-oxazolidine.

3,4-dihydro-1(2*H*)-naphthalenone (12.98 g≡ 88.8 mmole) and methanesulfonic acid (13.65 g≡ 142.0 mmole) in 1-butanol (60 ml) were heated to 50°C. In 2 minutes 3-ethyl-oxazolidine (13.46 g≡ 133.1 mmole) in 1-butanol (10 ml) was added. After 50 minutes at 80°C 2-methylimidazole (36.45 g ≡ 444.0 mmole) was added. After 2 hours at 120°C the reaction mixture was partly evaporated till 20 ml of 1-butanol was left over.

At 70°C, 60 ml of toluene and 40 ml of water were added to the residue. The layers were separated. The water layer was extracted with 60 ml of toluene. The combined toluene layers were washed three times with 80 ml of water.

The organic layer was evaporated to dryness and subsequently 100 ml of 1-butanol was added. To the resulting solution 10.0 ml of 36% m/m hydrochloric acid was added. The resulting solution was evaporated till an end volume of 50 ml. After stirring for 2 hours at 0°C the formed solid was filtered off and washed with 1-butanol and MTBE. Yield after drying: 17.30 g 3,4-dihydro-2-[(2-methyl-1*H*-imidazol-1-yl)methyl]-1(2*H*)-naphthalenone hydrochloride (70.4%). HPLC: ≥ 95%. ^{1}H NMR and MS: see Example 5.

Example 8. Reaction of 1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one with 3-oxazolidineethanol.

1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one (13.26 g≡66.5 mmole) and methanesulfonic acid (10.23 g≡106.4 mmole) in 1-butanol (45 ml) were heated to 90°C. In 2 minutes 11.68 g (99.8 mmole) of 3-oxazolidineethanol in 1-butanol (11 ml) was added.
After 50 minutes at 80°C 2-methylimidazole (27.32 g≡ 332.5 mmole) was added. After 2 hours at 120°C 180 ml of toluene and 120 ml of water were added at 80°C. The layers were separated. The water layer was extracted with 180 ml of toluene and 60 ml of 1-butanol. The combined organic layers were washed twice with 240 ml of water. The organic layer was evaporated to dryness. 150 ml of 1-butanol and 10 ml of 36% m/m hydrochloric acid were added to the residue. At 0°C crystallization soon occurred. After 1 hour at 0°C the formed crystals were filtered off, washed with 1-butanol and MTBE and subsequently dried: 15.39 g (70.1%) of 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1*H*-imidazol-1-yl)methyl]-4*H*-carbazol-4-one hydrochloride was isolated. HPLC: ≥ 95%. ^{1}H NMR [200 MHz, DMSO-d^6:$CDCl_3$ 4:1] δ 2.00 (1H,m), 2.20 (1H,m), 3.69 (3H,s), 3.09 (3H,m), 3.75 (3H,s), 4.30 (1H,dd), 4.67 (1H,dd), 7.23 (2H,m), 7.53 (2H,m), 7.69 (1H,d), 8.01 (1H, d). MS [ESI] MH^+ = 294. The mother liquor contained 3.19 g (14.5%) of product.

Example 9. Reaction of 1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one with 4,4-dimethyl-oxazolidine.

1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one (13.26 g ≡66.5 mmole) and methanesulfonic acid (10.23 g≡106.4 mmole) in 1-butanol (45 ml) were heated to 90°C. In 2 minutes 4,4-dimethyl-oxazolidine (10.09 g ≡ 99.9 mmole) in 1-butanol (8 ml) was added.
After 50 minutes at 80°C 2-methylimidazole (27.32 g ≡ 332.5 mmole) was added. After 2 hours at 120°C 180 ml of toluene and 120 ml of water were added at 80°C. The layers were separated. The water layer was extracted with 180 ml of toluene and 60 ml of 1-butanol. The combined organic layers were washed twice with 240 ml of water. The organic layer was evaporated to dryness. 150 ml of 1-butanol and 10 ml of 36% m/m hydrochloric acid were added to the residue. At 0°C crystallization soon occurred. After 1 hour at 0°C the formed crystals were filtered off, washed with 1-butanol and MTBE and subsequently dried: 10.02 g (45.7%) of 1,2,3,9-tetrahydro-9-

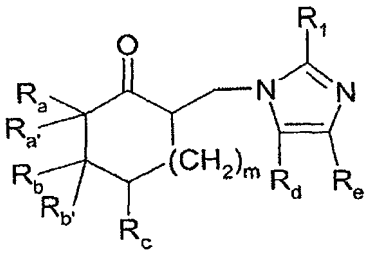
methyl-3-[(2-methyl-1*H*-imidazol-1-yl)methyl]-4*H*-carbazol-4-one hydrochloride. The mother liquor contained 2.70 g (12.3%) of product.
HPLC: ≥ 95%. NMR and MS: see Example 8.

Example 10. Reaction of 1,2,3,9-tetrahydro-9-methyl-4*H*-carbazol-4-one with 3-ethyl-oxazolidine.

1,2,3,9-tetrahydro-9-methyl-4*H*-carbazol-4-one (13.26 g≡66.5 mmole) and methanesulfonic acid (10.23 g≡106.4 mmole) in 1-butanol (45 ml) were heated to 90°C. In 2 minutes 3-ethyl-oxazolidine (10.09 g≡99.9 mmole) in 1-butanol (8 ml) was added. After 50 minutes at 80°C 2-methylimidazole (27.32 g≡ 332.5 mmole) was added. After 2 hours at 120°C 180 ml of toluene and 120 ml of water were added at 80°C. The layers were separated. The water layer was extracted with 180 ml of toluene and 60 ml of 1-butanol. The combined organic layers were washed twice with 240 ml of water. The organic layer was evaporated to dryness. 150 ml of 1-butanol and 10 ml of 36% m/m hydrochloric acid were added to the residue. At 0°C crystallization soon occurred. After 1 hour at 0°C the formed crystals were filtered off, washed with 1-butanol and MTBE and subsequently dried: 15.67 g (71.4%) of 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1*H*-imidazol-1-yl)methyl]-4*H*-carbazol-4-one hydrochloride was isolated. HPLC: ≥ 95%. NMR and MS: see Example 8. The mother liquor contained 2.06 g (9.4%) of product.

Claims

1. Method for the preparation of an imidazolyl compound of the general formula



(I)

wherein:

R_a and R_b each separately are $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$ alkoxyalkyl, optionally substituted aryl or heteroaryl;

or wherein R_a and R_b together form a further homocyclic or heterocyclic system comprising one or more rings;

$R_{a'}$ and $R_{b'}$ each are hydrogen or together form a carbon-carbon double bond, said carbon-carbon double bond optionally being part of an aromatic system;

R_c is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxyalkyl or halogen;

R_d is hydrogen or $(C_1\text{-}C_4)$alkyl;

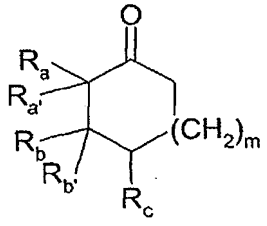
R_e is hydrogen or $(C_1\text{-}C_4)$alkyl;

m is 1 or 2; and

R_1 is hydrogen or $(C_1\text{-}C_4)$alkyl;

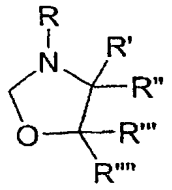
as well as its acid addition salt;

characterized in that a compound of the general formula



(II)

is reacted with a compound of the formula



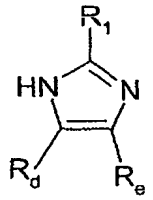
(III)

wherein:

R is a hydrogen, a (C_1-C_4)alkyl group optionally substituted with a hydroxygroup or an optionally substituted aryl group,

R', R", R"' and R"" each individually are a hydrogen or a (C_1-C_4)alkyl group;

followed by a reaction with a compound of the formula



(IV)

wherein R_1, R_d and R_e have the meanings defined above;

and optionally followed by a reaction with a suitable acid

2. Method according to claim 1, wherein

R_a, R_b, $R_{a'}$ $R_{b'}$ R, R', R", R"' and R"" have the same meanings as in claim 1;

R_c is hydrogen or (C_1-C_6)alkyl,

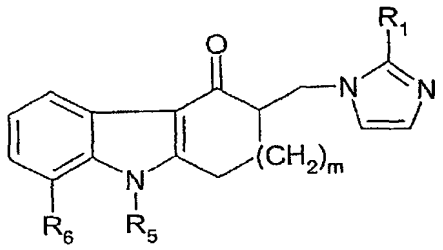
R_d is hydrogen or (C_1-C_4)alkyl;

R_e is hydrogen or (C_1-C_4)alkyl;

m is 1 or 2; and

R_1 is hydrogen, methyl of ethyl.

3. Method according to claim 1-2 for the preparation of an imidazolyl compound of the general formula



(Ia)

wherein:

m is 1 or 2;

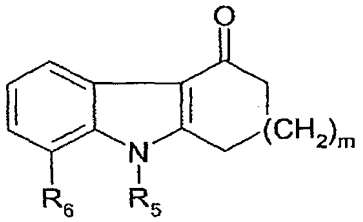
R_1 is hydrogen, methyl or ethyl; and

R_5 is a (C_1-C_4) alkyl

R_6 is a hydrogen or a (C_1-C_4)alkyl, or

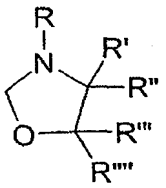
R_5 and R_6 together with the intermediate atoms form a 5, 6, or 7 membered ring, optionally substituted with one or two substituents selected from the group consisting of halogen, hydroxyl, (C_1-C_4)alkyl, C_1-C_4 alkoxyalkyl and C_1-C_4 alkoxy

as well as its pharmaceutically acceptable acid addition salt;
characterized in that a compound of the general formula



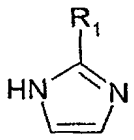
(IIa)

is reacted with a compound of the formula



(III)

wherein R, R', R", R'" and R"" have the same meanings as in claim 1;
followed by a reaction with a compound of the formula



(IVa)

4. Method according to claims 1-2, characterized in that R, R', R", R'" and R"" in formula (III) are 2-hydroxyethyl, hydrogen, hydrogen, hydrogen and hydrogen respectively.

5. Method as claimed in all preceding claims, characterized in that m=1 and that R_5 and R_6 together with the intermediate atoms form a 6-membered ring.

6. Method as claimed in claims 1-4, characterized in that m=1, that R_5 is methyl and that R_6 is hydrogen.

7. Method as claimed in any of the preceding claims, characterized in that the reaction is performed in an alcoholic solvent.

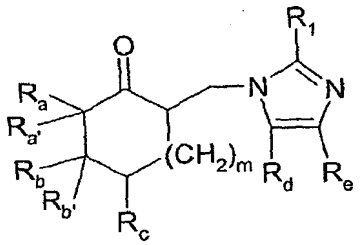
8. Method as claimed in claim 7, characterized in that the alcoholic solvent is 1-butanol.

9. Method as claimed in claims 1-6, characterized in that the reaction is performed in a mixture of an alcoholic solvent and an aromatic hydrocarbon

10. Method as claimed in claim 9, characterized in that said mixture is a mixture of methanol and chlorobenzene.

Abstract.

The present invention relates to a method for the preparation of an imidazolyl compound of the general formula



(I)

wherein:

R_a and R_b each separately are (C_1-C_6)alkyl, (C_1-C_6) alkoxyalkyl, optionally substituted aryl or heteroaryl;

or wherein R_a and R_b together form a further homocyclic or heterocyclic system comprising one or more rings;

$R_{a'}$ and $R_{b'}$ each are hydrogen or together form a carbon-carbon double bond, said carbon-carbon double bond optionally being part of an aromatic system;

R_c is hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxyalkyl or halogen;

R_d is hydrogen or (C_1-C_4)alkyl;

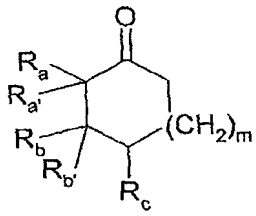
R_e is hydrogen or (C_1-C_4)alkyl;

m is 1 or 2; and

R_1 is hydrogen or (C_1-C_4)alkyl;

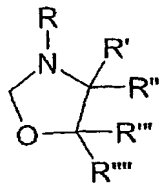
as well as its acid addition salt;

characterized in that a compound of the general formula



(II)

is reacted with a compound of the formula



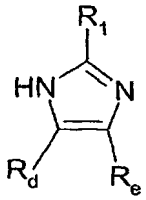
(III)

wherein:

R is a hydrogen, a (C_1-C_4)alkyl group optionally substituted with a hydroxygroup or an optionally substituted aryl group,

R', R", R"" and R"" each individually are a hydrogen or a (C_1-C_4)alkyl group;

followed by a reaction with a compound of the formula



(IV)

wherein R_1, R_d and R_e have the meanings defined above;

and optionally followed by a reaction with a suitable acid. De method according to the present invention is especially useful for the preparation of ondansetron and cilansetron.

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